

### REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action dated March 1, 2006 are respectfully requested. Applicants petition the Commissioner for a 3-month extension of time. A separate petition accompanies this amendment.

#### I. Rejections under 35 U.S.C. §103

Claims 1, 10-19 and 45 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Cottens *et al.* (U.S. Patent No. 5,912,253).

Applicants respectfully traverse these rejections.

##### A. The Present Invention

Claim 1 relates to a 42-O-ethoxyethyl rapamycin compound (claim 1). Claim 10 relates to a pharmaceutical composition comprising the 42-O-ethoxyethyl rapamycin compound. Claim 45 relates to a method of treating any of restenosis, wound healing, vascular injury, vascular inflammation, and transplant rejection, comprising administering the 42-O-ethoxyethyl rapamycin compound.

##### B. The Cited Art

COTTENS ET AL. describe demethoxy derivatives of rapamycin.

##### C. Analysis

###### 1. Claim 1

With regard to claim 1, which is directed to a 42-O-ethoxyethyl rapamycin<sup>1</sup> composition, Cottens *et al.* fail to show or suggest the particularly claimed compound. As noted by the Examiner, the closest compound disclosed is a 42-O-methoxyethyl

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<sup>1</sup> The convention for numbering rapamycin derivatives has been modified such that the 40-O as described in Cottens *et al.* is now designated 42-O.

rapamycin, which is a precursor listed in the synthesis of the disclosed demethoxy derivatives of rapamycin that are the basis of the Cottens *et al.* patent.

The Examiner invites the Applicants to show that the claimed compound possesses a property that the prior art compound does not show. The 42-O-(methoxyethyl) rapamycin compound as described in Cottens *et al.* has a small decrease in polarity (which relates to an increase in hydrophobicity) as compared to rapamycin. Of note, the small difference in polarity of the Cottens *et al.* compound and rapamycin results in nearly co-elution with unreacted rapamycin in chromatographic separations. Thus, the Cottens *et al.* compound is very difficult to purify.

Thus, one skilled in the art would expect that the composition of Cottens *et al.* would have similar effects as rapamycin as the effects relate to the hydrophobicity of the compounds. An increase in hydrophobicity reduces the aqueous solubility of the compound from the stent and increases the drug partition and uptake by local lipid rich tissue regions, thus providing improved local bioavailability of the compound.

In contrast to both the 42-O-(methoxyethyl) rapamycin and rapamycin, the present composition exhibits a far larger than expected increase in hydrophobicity (decrease in polarity). In fact, the present compound exhibits hydrophobicity that is at least 10X greater than rapamycin. The presently claimed compound was compared with rapamycin on the same metal stent/polymer platform. As seen in Table 1, the percentage of stenosis of the rapamycin coated stents was 3.7-2.9 times greater than the stents coated with the currently claimed composition. One skilled in the art would readily recognize a difference in properties between the 42-O-(methoxyethyl) rapamycin as described in Cottens *et al.* and the 42-O-(ethoxyethyl) rapamycin compound as presently claimed.

As an added benefit, the present composition is easier to purify than the 42-O-(methoxyethyl) rapamycin using chromatographic separations due to the larger than expected increase in hydrophobicity as compared to rapamycin.

The disclosure in Cottens *et al.* lends support to the above as it is described that derivatives of rapamycin that are similar in structure do not necessarily have

similar properties. Cottens *et al.* disclose that the "novel compounds" were "up to 3x more active than rapamycin" in the mixed lymphocyte reaction (see Col. 8, lines 60-61). The "novel compounds" were "up to 5x more active than rapamycin" in the IL-6 mediated proliferation test (see Col. 9, lines 15-16).

## 2. Claims 10-19

Claim 10 relates to a pharmaceutical composition comprising the 42-O-ethoxyethyl rapamycin compound and a carrier. Cottens *et al.* fail to show or suggest a pharmaceutical composition comprising such a compound. Instead, Cottens *et al.* is concerned with demethoxy derivatives of rapamycin. The 42-O-(2-methoxyethyl)-rapamycin as described in Example 8 is merely a reactant used to produce a demethoxy derivative. Accordingly, one skilled in the art would not be motivated to use the 42-O-(2-methoxyethyl)-rapamycin in a pharmaceutical composition much less to modify the compound and then use it in a composition. Instead, and based on the teaching of Cottens *et al.*, one skilled in the art would use demethoxy derivatives as they were demonstrated to be more efficacious than rapamycin.

## 3. Claim 45

Claim 45 relates to a method of treating any of:

- (i) restenosis;
- (ii) wound healing;
- (iii) vascular injury;
- (iv) vascular inflammation; and
- (v) transplant rejection

by administering a 42-O-(2-ethoxyethyl)-rapamycin. Similar to section 2, one skilled in the art would not be motivated to use the 42-O-(2-methoxyethyl)-rapamycin that is described as a precursor to the effective demethoxy derivatives in a method of treatment. Nor would one skilled in the art be motivated to modify the compound and then use it in a treatment method. Instead, and based on the teaching of Cottens *et al.*, one skilled in the art would use a demethoxy derivative as they were demonstrated to be more efficacious than rapamycin.

In view of the above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103.

**III. Statutory Double-Patenting Rejection**

Claims 1 was provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as claim 6 of co-pending Application No. 10/987,771. Applicants will address this rejection at such time as allowable claims are found in this or the co-owned application.

**IV. Obviousness-Type Double-Patenting Rejection**

Claims 1, 10-19, and 45 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being directed to an invention not patentably distinct from claims 1-5, 7-19, and 45 of co-owned U.S. Patent Application No. 10/987,771.

Applicants will address this rejection at such time as allowable claims are found in this or the co-owned application.

**Conclusion**

Applicants respectfully submit that the pending claims are in condition for immediate allowance. The undersigned invites the Examiner to call (650) 838-4410 with any questions or comments. The Commissioner is hereby authorized and requested to charge any deficiency in fees herein to Deposit Account No. 50-2207 to facilitate entry and consideration of this Amendment.

Respectfully submitted,  
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Date: Sept. 1, 2006

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